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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/646,628	08/22/2003	Bernard Moss	12804-027001	9682

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EXAMINER	
ZEMAN, ROBERT A	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/646,628	MOSS ET AL.	
	Examiner	Art Unit	
	Robert A. Zeman	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2007 and 04 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-35 and 39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-35 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3-12-2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3-12-2007 has been entered.

The amendment and response filed on 4-4-2007 are acknowledged. Claims 31 and 33-35 have been amended. Claims 36-38 have been canceled. Claim 39 has been added. Claims 31-35 and 39 are pending and currently under examination.

Objections Withdrawn

The objection to the drawings filed on 8-22-2003 is withdrawn in light of the replacement drawing filed on 4-16-2007.

The objection to claim 31 due to its containing an obvious typographical error within the term "cytoplamic" is withdrawn in light of the amendment thereto.

Objections Maintained

Specification

The disclosure is still objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see page 19 for example). Applicant is required to check the

specification of all instances of hyperlinks and/or browser-executable code and them. See MPEP § 608.01. It should be noted that Applicant did not address this objection in his response.

The use of the trademarks Biojector and cytofix/cytoperm has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Applicant is required to check the specification for all instances of trademarks/tradenames being used. It should be noted that Applicant did not address this objection in his response.

Claim Rejections Withdrawn

The rejection of claim 31 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrase "but lacking or all or part of the cytoplasmic domain of gp41" is withdrawn in light of the amendment thereto.

The rejection of claims 33-38 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in lieu of the rejection set forth below.

The rejection of claims 31-38 under 35 U.S.C. 103(a) as being unpatentable over Kent et al. (Journal of Virology 1998, Vol. 72, No. 12, pages 10180-10188 – IDS) in view of Small et al. (U.S. Patent 5,676,950 – IDS) and Gao et al. (Journal of Molecular Biology, 1998, Vol. 277, pages 559-572) is withdrawn.

New Grounds of Rejection

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description Rejection

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claims 31-34 and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) still contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's arguments as they pertain to this rejection are addressed below.

Applicant argues:

1. The instant claims have been amended to recite HIV-1.

2. The CAFC in their decisions regarding *Invitrogen Corporation v. Clontech Laboratories, Inc* and *Capon v. Eshhar* that whether a disclosure meets the written description requirement depends on the knowledge of those skilled in the art.

3. The HIV genome and proteins expressed by HIV are extremely well studied and the genomes of many different HIV strains from a variety of clades have been sequenced in whole or in part (and were as of the priority date of the instant application).

4. HIV Pol has been extremely well studied.

5. The specification discloses that HIV sequences can be found in various sequence databases.

6. The HIV Sequences Compendium 2000 discloses nearly 100 HIV pol sequences from various clades that have been aligned with the HXB2 sequence providing a means to identify other pol variants that have a mutation that inhibits reverse transcriptase activity.

7. Said alignments identify domains associated with RNaseH activity and integrase activity.

8. Numerous mutations within HIV pol that inhibit reverse transcriptase activity, RNaseH activity or strand transfer activity (as demonstrated by the cited references) are known to those skilled in the art.

9. Given the large number of HIV sequences known to researchers, Applicant's description of mutations in HIV HXB2 pol that lead to reduced reverse transcriptase activity, reduced strand transfer activity or reduced RNaseH activity is sufficient to meet the written description requirement.

Applicant's arguments have been fully considered and deemed non-persuasive.

With regard to Point 1, limiting the instant claims to recite HIV-1 is insufficient to overcome the aforementioned rejection.

With regard to Point 2, the crux of the *Invetrogen* and *Capon* decisions is what is known in the art. In the *Invitrogen* case the CAFC concluded that the district court was correct when it ruled that (1) the common written description, (2) testimony from Invitrogen's expert, Dr.

Champouix and (3) an article by Johnson et al.,'83 Proc. Natn'l Acad: Sci. USA 7648-52: 7651 (1986), established a sufficiently known correlation between RNase H activity in RT (function) and the RT gene made by deletion mutation (structure) to satisfy the PTO test for written description. The court concluded that the undisputed evidence was entirely one sided in favor of Invitrogen, and granted partial summary judgment, ruling that the claims at issue were not invalid for lack of written description. (see page 1072 of decision).

In the *Capon* decision, the CAFC stated "In summary, the Board erred in ruling that §112 imposes a *per se* rule requiring recitation in the specification of the nucleotide of claimed DNA when that sequence is already known in the field. However, the Board did not explore the support for each of the claims of both parties in view of the specific examples and general teachings in the specifications and the known science with application of precedent guiding review of the scope of the claims."

In both cases the CAFC determined that the correlation between structure and function, required to meet the written description requirements, where known in the art. This is not the case with regard to the instant claims as the specific immunoepitopes of HIV-1 Gag, Pol and Env which induce a CD8+ T cell immune response in a primate when said primate is primed with the recited nucleic acid and boosted with the claimed recombinant MVA virus are not known in the art. Moreover, the specification is remiss in describing what mutations can be made that will not only result in the desired alteration in protein function (as set forth in claims 33-35) but which of those alterations would allow for a directed CD8+ T cell immune response to any or all HIV Gag, Pol or Env proteins. Consequently, neither the *Invitrogen* nor the *Capon* decisions are germane to the instant rejection.

With regard to Points 4-6, the rejection is based on which residues can be mutated to obtain an inhibition of a given activity and induce a specific immune response. Other than the mutations of residues 185, 266, 478 of HIV-1 HXB2, the specification is silent as to what mutations would result in the desired reduction in a given pol activity. Hence, there is no correlation between structure and function as required to by the written description requirement. Moreover, with regard to claims 36-38 there is no baseline sequence recited so the recited residues have no clear-cut meaning.

With regard to Point 7-8, adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The protein itself is required.

With regard to Point 9, the amended instant claims encompass HIV-1 proteins that can induce a directed CD8+ T cell response to the Gag, Pol or Env protein of any or all HIV strains (i.e. HIV-1, HIV-2, HIV-3 etc) while Applicant's arguments are based on HIV-1 only. Additionally, Applicant's arguments (and the Examples in the specification) are based on alignments using the HIV-1 HXB2 pol genome that is not part of the claims. Moreover, due to the high degree of variability in HIV genomes due to the 5-10% error rate associated with reverse transcription of the HIV RNA genome, one would not be able to predict whether a given mutation would have the same effect in all HIV strains. Consequently, since there is no correlation between structure and the claimed function, it is deemed the written description requirement has not been met.

Finally, as claims recite specific "domains", it is deemed that the baseline HIV sequences constitute essential material. The MPEP states:

> **608.01(p)**
> Newly filed applications obviously failing to disclose an invention with the clarity

required are discussed in MPEP § 702.01.A disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which the invention pertains to make and use the invention as of its filing date. *In re Glass,* 492 F.2d 1228, 181 USPQ 31(CCPA 1974).

An application as filed must be complete in itself in order to comply with 35 U.S.C. 112. Material nevertheless may be incorporated by reference, *Ex parte Schwarze*, 151 USPQ 426 (Bd. App. 1966). An application for a patent when filed may incorporate "essential material" by reference to (1) a U.S. patent, (2) a U.S. patent application publication, or (3) a pending U.S. application, subject to the conditions set forth below.
"Essential material" is defined as that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode (35 U.S.C. 112). In any application which is to issue as a U.S. patent, essential material **may not be** incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, **(2) non-patent publications**, (3) a U.S. patent or application which itself incorporates "essential material" by reference, or (4) a foreign application.

The specification discloses *gag, pol* and *env* genes and their incorporation into recombinant MVA viruses. However, the aforementioned claims are directed to sequences encoding proteins that have the ability to induce a directed CD8+ T cell immune response against Gag, Pol or Env of any or all HIV strains **and** have inhibited reverse transcriptase activity (claim 33), inhibited strand transfer activity (claim 34) or inhibited RNaseH activity (claim 35) encompassing mutated sequences. allelic variants, splice variants, sequences that have a recited degree of identity (similarity. homology), and so forth. None of these sequences meet the written description provision of 35 USC 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by the claim.

To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and

distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession the claimed invention. To adequately describe the genus of *"immunogenic* compositions" comprising nucleic acids encoding the recited HIV-1 proteins and recombinant MVA viruses expressing said HIV-1 proteins, Applicant must not only describe which mutations would result in the altered protein functions encompassed by claims 33-35), they must adequately describe the antigenic determinants (immunoepitopes) that elicit CD8+ T cell immune response directed against any or all HIV Gag, Pol or in a primate.

The specification, however, does not disclose distinguishing and identifying features of a representative number of members of the genus of immunogenic compositions to which the claims are drawn, such as a correlation between the structure of the surface marker and its recited function (to elicit an CD8+ T cell immune response directed against HIV Gag, Pol or Env), so that the skilled artisan could immediately envision, or recognize at least a substantial number of members of the claimed genus of immunogenic compositions. Moreover, the specification fails to disclose which amino acid residues (if any) are essential to the function of the immunoepitope or which amino acids might be replaced so that the resultant immunoepitope retains the activity of its parent, or by which other amino acids the essential amino acids might be replaced so that the resultant immunoepitope retains the activity of its parent. Therefore, since the specification fails to adequately describe at least a substantial number of members of the genus of immunoepitopes to which the claims are based; the specification fails to adequately describe at least a substantial number of members of the claimed genus of immunogenic compositions capable of stimulating a CD8+ T cell immune response in an primate to HIV Gag, Pol or Env.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the

written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description'' Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual

reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. As evidenced by Greenspan et al. (*Nature Biotechnology* 7: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit a directed immune response to a given pathogen can only be identified empirically. Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of immunoepitopes, the skilled artisan could not immediately recognize or distinguish members of the claimed genus of immunogenic compositions capable of stimulating directed CD8+ T cell immune response in an primate *to any*

or all HIV Gag, Pol or Env proteins. Therefore, because the art is unpredictable, in accordance with the *Guidelines*, the description of surface markers/ immunoepitopes (antigenic determinants) is not deemed representative of the genus of immunogenic compositions to which the claims refer.

Additionally, the specification is remiss in describing what mutations can be made that will not only result in the desired alteration in protein function (as set forth in claims 33-35) but which of those alterations would allow for a directed CD8+ T cell immune response to any or all HIV Gag, Pol or Env proteins.

Enablement Rejection

Claims 31-35 and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The rejected claims are drawn to are directed to nucleic acids with sequences encoding proteins that have the ability to induce a directed CD8+ T cell immune response against Gag, Pol or Env of any or all HIV strains **and optionally** have inhibited reverse transcriptase activity (claim 33), inhibited strand transfer activity (claim 34) or inhibited RNaseH activity (claim 35). However, Applicant has failed to demonstrate any immunoepitopes of HIV-1 Gag, Pol or Env that are capable of inducing a directed CD8+ T cell immune response to the Gag, Pol or Env of any or all HIV strains. The specification is equally silent as to which mutations can be made to the HIV-1 Gag, Pol or Env proteins that would result in the recited altered protein function and still be able to

induce the claimed immune response. While the skill in the art of immunology is high, to date, prediction of a specific immune response for any given composition in any given animal is quite unpredictable. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome **and form immunoepitopes**. Bowie et al. further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Additionally, as evidenced by Greenspan et al. (*Nature Biotechnology* 7: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it

follows that the immunoepitopes that can elicit a protective immune response to a given pathogen can only be identified empirically. This constitutes undue experimentation. Therefore, given the lack of success in the art, the lack of working examples commensurate in scope to the claimed invention and the unpredictability of the generation of a directed immune response, the specification, as filed, does not provide enablement for immunogenic compositions comprising nucleic acids encoding HIV-1 Gag, Pol or Env and recombinant MVA viruses expressing said HIV-1 proteins.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (571) 272-0866. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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ROBERT A. ZEMAN
PRIMARY EXAMINER
July 8, 2007